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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
08/477,097	06/07/95	LIVINGSTON	P	43016-B/JPW/

HM21/0415

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EXAMINER	
CAPUTA, A	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 04/15/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No. 08/477,097	Applicant(s) Livingston et al.
	Examiner Anthony C. Caputa	Group Art Unit 1645

☒ Responsive to communication(s) filed on *16 Jan 1998*.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *53-71* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *53-71* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1645.

2. Applicants' amendment dated 1/16/98 was entered as Paper No. 17. Claims 53-71 are pending.

Specification

3. The prior objection to the disclosure is maintained for the reasons as set forth in the last Office Action mailed 6/10/96 (see Paper No. 9).

Applicants submit they will submit a new Figure 6B to overcome the rejection when the case is in condition for allowance. Until applicants submit a proper Figure said objection is maintained.

Double Patenting

4. Claims 53-71 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims 1-4, 6-20, and 44-52 of copending Application No. 08/475,784 for the reason set forth in the last Office Action.

5. Claims 53-71 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over clams 44 and 46-56 of copending Application Nos. 08/477,147 and 08/481,809.

Although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons set forth in the prior Office Actions.

Applicants argue that they will add new claims in USSN 08/475,784; 08/477,147; and 08/481,089 and that they believe the added new claims in the applications will obviate the obvious type double patenting. Applicants arguments are noted. However, until said claims are added said rejection is maintained for the reasons of record. Furthermore, the Examiner suggests that applicants provide a copy of the claims in the copending applications in the next Office Action.

Claim Rejections - 35 USC § 112

6. Claims 53-56, and 58-71 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons set forth in the Office Action mailed 6/10/96 (see Paper No. 9).

Applicants' amendment is sufficient to obviate the objection to the specification for: 1) the use of other gangliosides or chemically modified gangliosides; and 2) use of the claimed product as a vaccine. However, the specification provides insufficient guidance of how to use derivatives of KLH as recited. Applicants assert that by routine experimentation one skilled in the art is enabled to make derivatives of KLH (see Applicants arguments on Paper No. 12; page 4). Applicants assert that the derivatives of KLH can be tested using the KLH disclosed in the specification. Applicants arguments are not persuasive.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al.). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduce the biological activity of the mitogen (see Lazar et al.). Rudinger et al. Teaches "particular amino acids and sequences for

different aspects of biological activity can not be predicted a *priori* but must be determined from case to case by painstakingly experimental study" (see page 6). Salgaller et al teach modifications (i.e. deletions) of the amino acid structure of peptide can alter the activity of the protein. Fox et al. Teach methods for determining fragments which have antigenic activity is unpredictable. These references demonstrate that a even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. In view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad or derivatives and fragments encompassed in the scope of the claims one skilled in the art would be forced into undue experimentation in order to practice broadly the claimed invention.

Contrary to applicants arguments it is reasonable to conclude an undue burden is required to screen for positions within the sequence where amino acid modifications (i.e. additions, deletions, or modifications) can be made with a reasonable expectation of success in obtaining similar activity/utility are limited and the result of such modifications is unpredictable as exemplified by the teachings of Lazar et al., Burgess et al., Rudinger et al., and Salgaller et al. These references demonstrate that a even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein.

The specification does not support the broad scope of the claims which encompass a multitude of analogs or equivalents because the specification does **not** disclose the following :

- the general tolerance to modification and extent of such tolerance;
- specific positions which can be predictably modified; and
- the specification provide essentially no guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have **not** provided sufficient guidance to enable one skilled in the art to make and use the claimed derivatives in a manner reasonably correlated with the scope of the claims

broadly including any number of deletions, additions, and/or substitutions of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int. 1986).

Applicants cite to page 12, lines 4-13 of the specification for support of using derivatives of KLH. Said disclosure is not commensurate in scope with the claimed invention. Said cite makes reference only to linking KLH to an "immunological adjuvant" **and not** amino acid modifications (i.e deletions, substitutions) of KLH. As set forth above the scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). For the reason set forth above and in the last Office Action said rejection is maintained.

7. Claims 53-71 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The original specification does not provide an adequate written description of conjugating a ceramide portion of the GM2 or GD2. The specification as originally filed only provides support of conjugating GD3 by the ceramide portion (see page 32). The Examiner acknowledges applicants remarks for support of claimed subject matter. However, applicants remarks are directed to claims canceled. The Examiner invites applicants to point by page and line number for conjugating GM2 or GD3 by the ceramide portion as newly submitted.

8. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Ritter et al. 1990 (Exhibit 13) discloses of a GD3 amide derivative and that said derivatives had the highest antibody response (see page 38).

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Anthony C. Caputa, whose telephone number is (703)-308-3995. The examiner can be reached on Monday-Thursday from 8:30 AM-6:00 PM. The examiner can be reached on alternate Fridays. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703)-308-0196. Papers related to this application may be submitted to Art Unit 1645 by facsimile transmission. The faxing of such papers must conform with the notice published in the official Gazette 1096 OG 30 (November 15, 1989). The Fax number is (703)-308-4242.

Anthony C. Caputa, Ph.D.
13 April 1998

ANTHONY C. CAPUTA
PRIMARY EXAMINER